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=> d his

     (FILE 'HOME' ENTERED AT 09:38:31 ON 16 APR 2009)

     FILE 'CAPLUS' ENTERED AT 09:38:44 ON 16 APR 2009
L1             1 S US20070142635/PN
                 SELECT RN L1 1-

     FILE 'REGISTRY' ENTERED AT 09:39:09 ON 16 APR 2009
L2            31 S E1-31
L3            16 S L2 AND 6-7/SZ
L4            15 S L2 NOT L3
L5       1899364 S 46.195/RID
L6             3 S L4 AND L5
L7            12 S L4 NOT L6
L8            23 S C18 H31 N3 O8/MF
L9          1017 S C7 H14 N2 O/MF
L10           50 S C12 H25 N3 O4/MF
L11          782 S C12 H22 N2 O3/MF
L12            1 S L7 AND L8
L13            1 S L7 AND L9
L14            1 S L7 AND L10
L15            1 S L7 AND L11
L16            8 S L7 NOT (L12 OR L13 OR L14 OR L15)

     FILE 'CAPLUS' ENTERED AT 09:44:12 ON 16 APR 2009
L17            9 S L3
L18            4 S L6
L19            4 S L12
L20            3 S L13
L21            4 S L14
L22            4 S L15
L23            9 S L17 OR L18 OR L19 OR L20 OR L21 OR L22

=> d ibib abs hitstr total
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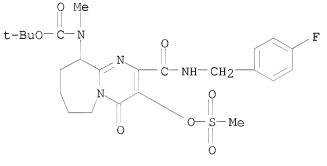
L23 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:1524819 CAPLUS
DOCUMENT NUMBER: 150:121598
TITLE: Catalytic asymmetric synthesis of an HIV integrase inhibitor
AUTHOR(S): Zhong, Yong-Li; Krska, Shane W.; Zhou, Hua; Reamer, Robert A.; Lee, Jaemoon; Sun, Yongkui; Askin, David
CORPORATE SOURCE: Department of Process Research, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Organic Letters (2009), 11(2), 369-372
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB An efficient synthesis of HIV integrase inhibitor I via a unique asym. hydrogenation of a mixture of imines/enamine is described. Hydrogenation of the imines/enamine by a Rh(I)-Josiphos complex afforded II in 90% yield and 90% ee. Amide formation completed the synthesis of I in 58% overall yield from III, which is readily available from 3,4-dihydro-2H-pyran in a seven-step sequence. A deuterium labeling study suggests the asym. hydrogenation proceeds predominantly via the enamine tautomer.

IT 857672-38-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(stereoselective preparation of tetrahydropyrimidoazepinone derivative as HIV
integrase inhibitor via hydrolysis of mesylated bicyclic pyrimidinone followed by rhodium-catalyzed asym. hydrogenation and amidation)

RN 857672-38-9 CAPLUS
CN Carbamic acid, [2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-[(methylsulfonyl)oxy]-4-oxopyrimido[1,2-a]azepin-10-yl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

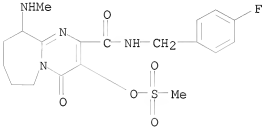


IT 857672-39-0P 857672-43-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(stereoselective preparation of tetrahydropyrimidoazepinone derivative as HIV

integrase inhibitor via hydrolysis of mesylated bicyclic pyrimidinone followed by rhodium-catalyzed asym. hydrogenation and amidation)

RN 857672-39-0 CAPLUS

CN Pyrimido[1,2-a]azepine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-10-(methylamino)-3-[(methylsulfonyl)oxy]-4-oxo-, hydrochloride (1:1) (CA INDEX NAME)

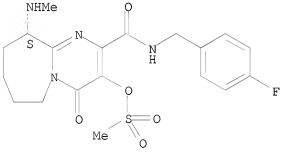


● HCl

RN 857672-43-6 CAPLUS

CN Pyrimido[1,2-a]azepine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-10-(methylamino)-3-[(methylsulfonyl)oxy]-4-oxo-, (10S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 724444-40-0P

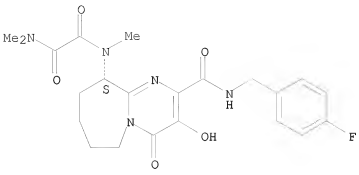
RL: SPN (Synthetic preparation); PREP (Preparation)

(stereoselective preparation of tetrahydropyrimidoazepinone derivative as HIV integrase inhibitor via hydrolysis of mesylated bicyclic pyrimidinone followed by rhodium-catalyzed asym. hydrogenation and amidation)

RN 724444-40-0 CAPLUS

CN Ethanediamide, N1-[(10S)-2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]-N1,N2,N2-trimethyl- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

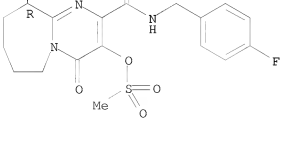
L23 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:1319872 CAPLUS
DOCUMENT NUMBER: 150:7236
TITLE: Practical Synthesis of a HIV Integrase Inhibitor
AUTHOR(S): Zhong, Yong-Li; Pipik, Brenda; Lee, Jaemoon; Kohmura, Yoshinori; Okada, Shigemitsu; Igawa, Kazunobu; Kadowaki, Chie; Takezawa, Akihiro; Kato, Shinji; Conlon, David A.; Zhou, Hua; King, Anthony O.; Reamer, Robert A.; Gauthier, Donald R. Jr.; Askin, David
CORPORATE SOURCE: Department of Process Research, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Organic Process Research & Development (2008), 12(6), 1245-1252
CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A practical and efficient synthesis of the potent HIV integrase inhibitor [(10S)-2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]trimethyl-ethanediamide (1) is described. Starting from readily available 3,4-dihydro-2H-pyran, the six-step synthesis features a through process without purification of any of the intermediates until isolation of crystalline intermediate bicyclic hydroxypyrimidinone. After deprotection and classical resolution, the amine hydrochloride was isolated with excellent enantio-purity. A final amide coupling completed the synthesis of 1 in 7.6% overall yield from DHP. This chromatog.-free route is more cost effective and increases the overall yield by nearly 3 times when compared with the original Med Chem synthetic route. This improved chemical was used successfully to prepare multi-kilogram quantities of integrase inhibitor 1.

IT 857672-41-4P 857672-42-5P
RL: BYP (Byproduct); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(scale-up of practical synthesis steps and purification of pyrimidoazepine carboxylate HIV integrase inhibitor)

RN 857672-41-4 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-10-(methylamino)-3-[(methylsulfonyl)oxy]-4-oxo-, (10R)- (CA INDEX NAME)

Absolute stereochemistry.



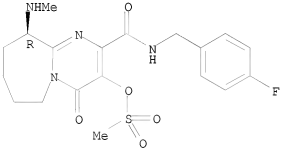
RN 857672-42-5 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, (2S,3S)-, compd. with

(10R)-N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-10-(methylamino)-3-[(methylsulfonyl)oxy]-4-oxopyrimido[1,2-a]azepine-2-carboxamide (1:2)
(9CI) (CA INDEX NAME)

CM 1

CRN 857672-41-4
CMF C19 H23 F N4 O5 S

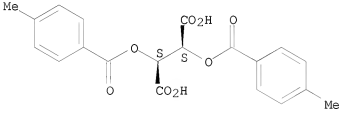
Absolute stereochemistry.



CM 2

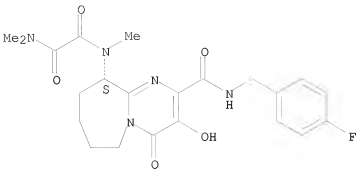
CRN 32634-68-7
CMF C20 H18 O8

Absolute stereochemistry. Rotation (+).



IT 724444-40-0P
RL: IMF (Industrial manufacture); PRP (Properties); PREP (Preparation)
(scale-up of practical synthesis steps and purification of pyrimidoazepine carboxylate HIV integrase inhibitor)
RN 724444-40-0 CAPLUS
CN Ethanediamide, N1-[(10S)-2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]-N1,N2,N2-trimethyl- (CA INDEX NAME)

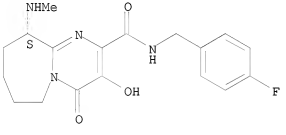
Absolute stereochemistry. Rotation (-).



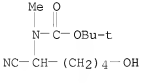
IT 724445-90-3P 724445-95-8P 724445-97-0P
724445-98-1P 724446-00-8P 724446-08-6P
724446-10-0P 724783-88-4P 857672-38-9P
857672-39-0P 857672-40-3P 857672-44-7P
857859-45-1P
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(scale-up of practical synthesis steps and purification of pyrimidoazepine carboxylate HIV integrase inhibitor)

RN 724445-90-3 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-10-(methylamino)-4-oxo-, (10S)- (CA INDEX NAME)

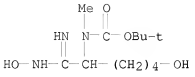
Absolute stereochemistry. Rotation (-).



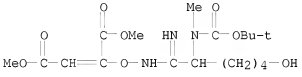
RN 724445-95-8 CAPLUS
CN Carbamic acid, (1-cyano-5-hydroxypentyl)methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



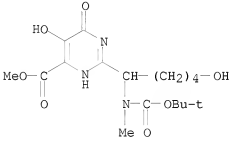
RN 724445-97-0 CAPLUS
CN Carbamic acid, [5-hydroxy-1-[(hydroxyamino)iminomethyl]pentyl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



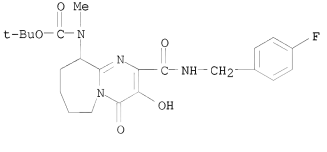
RN 724445-98-1 CAPLUS
CN 2-Butenedioic acid, 2-[[[2-[[(1,1-dimethylethoxy)carbonyl]methylamino]-6-hydroxy-1-iminohexyl]amino]oxy]-, 1,4-dimethyl ester (CA INDEX NAME)



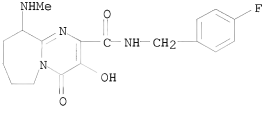
RN 724446-00-8 CAPLUS
CN 4-Pyrimidinecarboxylic acid, 2-[1-[[(1,1-dimethylethoxy)carbonyl]methylamino]-5-hydroxypentyl]-1,6-dihydro-5-hydroxy-6-oxo-, methyl ester (CA INDEX NAME)



RN 724446-08-6 CAPLUS
CN Carbamic acid, [2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

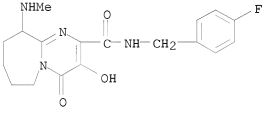


RN 724446-10-0 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide,
N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-10-(methylamino)-4-oxo-, hydrochloride (1:1) (CA INDEX NAME)

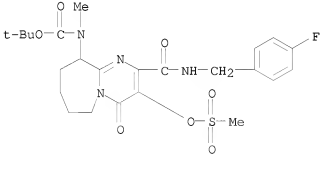


● HCl

RN 724783-88-4 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide,
N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-10-(methylamino)-4-oxo- (CA INDEX NAME)

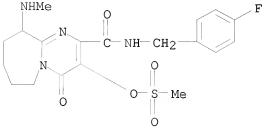


RN 857672-38-9 CAPLUS
CN Carbamic acid, [2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-[(methylsulfonyl)oxy]-4-oxopyrimido[1,2-a]azepin-10-yl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



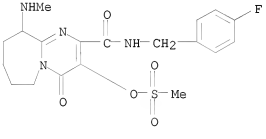
RN 857672-39-0 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide,

N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-10-(methylamino)-3-[(methylsulfonyl)oxy]-4-oxo-, hydrochloride (1:1) (CA INDEX NAME)



● HCl

RN 857672-40-3 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-10-(methylamino)-3-[(methylsulfonyl)oxy]-4-oxo- (CA INDEX NAME)

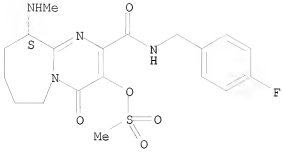


RN 857672-44-7 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, (2S,3S)-, compd. with (10S)-N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-10-(methylamino)-3-[(methylsulfonyl)oxy]-4-oxopyrimido[1,2-a]azepine-2-carboxamide (1:2) (9CI) (CA INDEX NAME)

CM 1

CRN 857672-43-6
CMF C19 H23 F N4 O5 S

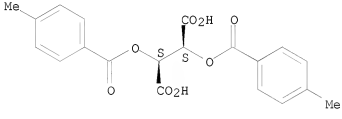
Absolute stereochemistry.



CM 2

CRN 32634-68-7
CMF C20 H18 O8

Absolute stereochemistry. Rotation (+).

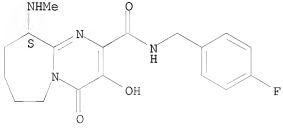


RN 857859-45-1 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, (2R,3R)-, compd. with (10S)-N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-10-(methylamino)-4-oxopyrimido[1,2-a]azepine-2-carboxamide (1:2) (9CI) (CA INDEX NAME)

CM 1

CRN 724445-90-3
CMF C18 H21 F N4 O3

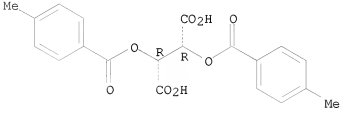
Absolute stereochemistry. Rotation (-).



CM 2

CRN 32634-66-5
CMF C20 H18 O8

Absolute stereochemistry. Rotation (-).



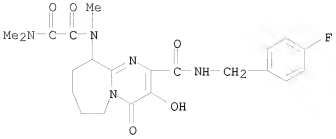
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:1311767 CAPLUS
DOCUMENT NUMBER: 150:51183
TITLE: Resistance mutations in human immunodeficiency virus type 1 integrase selected with elvitegravir confer reduced susceptibility to a wide range of integrase inhibitors
AUTHOR(S): Goethals, Olivia; Clayton, Reginald; Van Ginderen, Marcia; Vereycken, Inge; Wagemans, Elisabeth; Geluykens, Peggy; Dockx, Koen; Strijbos, Rudy; Smits, Veerle; Vos, Ann; Meersseman, Geert; Jochmans, Dirk; Vermeire, Kurt; Schols, Dominique; Hallenberger, Sabine; Hertogs, Kurt
CORPORATE SOURCE: Tibotec BVBA, Mechelen, Belg.
SOURCE: Journal of Virology (2008), 82(21), 10366-10374
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Integration of viral DNA into the host chromosome is an essential step in the life cycle of retroviruses and is facilitated by the viral integrase enzyme. The first generation of integrase inhibitors recently approved or currently in late-stage clin. trials shows great promise for the treatment of human immunodeficiency virus (HIV) infection, but virus is expected to develop resistance to these drugs. Therefore, we used a novel resistance selection protocol to follow the emergence of resistant HIV in the presence of the integrase inhibitor elvitegravir (GS-9137). We find the primary resistance-conferring mutations to be Q148R, E92Q, and T66I and demonstrate that they confer a reduction in susceptibility not only to elvitegravir but also to raltegravir (MK-0518) and other integrase inhibitors. The locations of the mutations are highlighted in the catalytic sites of integrase, and we correlate the mutations with expected drug-protein contacts. In addition, mutations that do not confer reduced susceptibility when present alone (H114Y, L74M, R20K, A128T, E138K, and S230R) are also discussed in relation to their position in the catalytic core domain and their proximity to known structural features of integrase. These data broaden the understanding of antiviral resistance against integrase inhibitors and may give insight facilitating the discovery of second-generation compds.

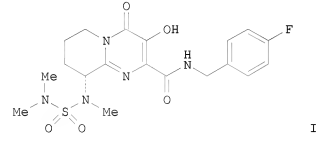
IT 724444-38-6
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(resistance mutations in human immunodeficiency virus type 1 integrase selected with elvitegravir confer reduced susceptibility to a wide range of integrase inhibitors)

RN 724444-38-6 CAPLUS
CN Ethanediamide, N1-[2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]-N1,N2,N2-trimethyl- (CA INDEX NAME)

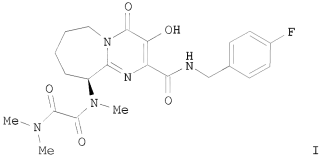


REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:102187 CAPLUS
DOCUMENT NUMBER: 148:331633
TITLE: Design and Synthesis of Bicyclic Pyrimidinones as Potent and Orally Bioavailable HIV-1 Integrase Inhibitors
AUTHOR(S): Muraglia, Ester; Kinzel, Olaf; Gardelli, Cristina; Crescenzi, Benedetta; Donghi, Monica; Ferrara, Marco; Nizi, Emanuela; Orvieto, Federica; Pescatore, Giovanna; Laufer, Ralph; Gonzalez-Paz, Odalys; Di Marco, Annalise; Fiore, Fabrizio; Monteagudo, Edith; Fonsi, Massimiliano; Felock, Peter J.; Rowley, Michael; Summa, Vincenzo
CORPORATE SOURCE: IRBM Merck Research Laboratories Rome, Rome, 00040, Italy
SOURCE: Journal of Medicinal Chemistry (2008), 51(4), 861-874
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 148:331633
GI



I



II

AB HIV integrase is one of the three enzymes encoded by HIV genome and is essential for viral replication, but integrase inhibitors as marketed drugs have just very recently started to emerge. In this study, the evolution from the N-methylpyrimidinone structure to bicyclic

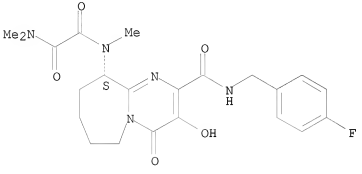
pyrimidinones, e.g., I and II, is shown. Introduction of a suitably substituted amino moiety modulated the phys.-chemical properties of the mols. and conferred nanomolar activity in the inhibition of spread of HIV-1 infection in cell culture. An extensive SAR study led to sulfamide I, which inhibited the strand transfer with an IC50 of 7 nM and HIV infection in MT4 cells with a CIC95 of 44 nM, and ketoamide II that inhibited strand transfer with an IC50 of 12 nM and the HIV infection in MT4 cells with a CIC95 of 13 nM and exhibited a good pharmacokinetic profile when dosed orally to preclin. species.

IT 724444-40-0P
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation, HIV-1 integrase inhibitory activity, and SAR of bicyclic pyrimidinones)

RN 724444-40-0 CAPLUS

CN Ethanediamide, N1-[(10S)-2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]-N1,N2,N2-trimethyl- (CA INDEX NAME)

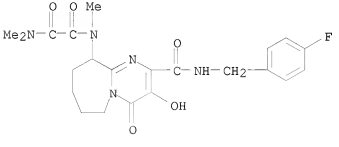
Absolute stereochemistry. Rotation (-).



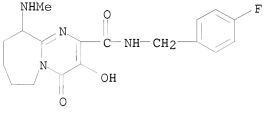
IT 724444-38-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation, HIV-1 integrase inhibitory activity, and SAR of bicyclic pyrimidinones)

RN 724444-38-6 CAPLUS

CN Ethanediamide, N1-[2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]-N1,N2,N2-trimethyl- (CA INDEX NAME)

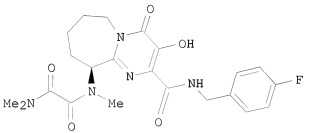


IT 724783-88-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, HIV-1 integrase inhibitory activity, and SAR of bicyclic pyrimidinones)
RN 724783-88-4 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-10-(methylamino)-4-oxo- (CA INDEX NAME)



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:1252417 CAPLUS
DOCUMENT NUMBER: 148:78968
TITLE: Synthesis of a hexahydropyrimido[1,2-a]azepine-2-carboxamide derivative useful as an HIV integrase inhibitor
AUTHOR(S): Ferrara, Marco; Crescenzi, Benedetta; Donghi, Monica; Muraglia, Ester; Nizi, Emanuela; Pesci, Silvia; Summa, Vincenzo; Gardelli, Cristina
CORPORATE SOURCE: Department of Medicinal Chemistry, IRBM-MRL Rome, Pomezia (Rome), 00040, Italy
SOURCE: Tetrahedron Letters (2007), 48(47), 8379-8382
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 148:78968
GI



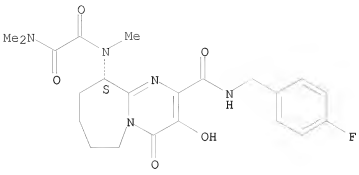
I

AB The hexahydropyrimido[1,2-a]azepine-2-carboxamide derivative I could be obtained by three synthetic strategies, which allowed access to multigram amts. of material of high purity and ee. Two strategies involved alternative approaches to the bicyclic pyrimidone core, with the most efficient one being a two-step sequence from com. available starting materials exploiting a little precedented cyclization reaction. The remaining steps to I included an efficient crystallization of an intermediate as a single stereoisomer. An alternative strategy employing a chiral starting material led to products of low optical purity but allowed the assignment of the configuration of the stereogenic center of I.

IT 724444-40-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(stereoselective synthesis of a hexahydropyrimido[1,2-a]azepine-2-carboxamide derivative useful as an HIV integrase inhibitor)

RN 724444-40-0 CAPLUS
CN Ethanediamide, N1-[(10S)-2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]-N1,N2,N2-trimethyl- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



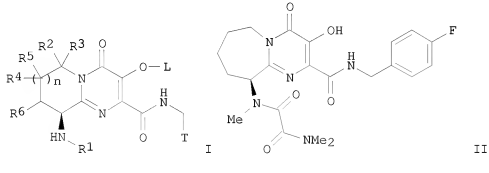
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:542616 CAPLUS
DOCUMENT NUMBER: 145:46081
TITLE: Process for preparation of chiral hexahydropyrimido[1,2-a]azepine-2-carboxamides as HIV integrase inhibitors
INVENTOR(S): Zhong, Yong-Li; Krska, Shane W.; Lee, Jaemoon
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006060225	A2	20060608	WO 2005-US42211	20051118
WO 2006060225	A3	20061012		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-630322P P 20041123
OTHER SOURCE(S): CASREACT 145:46081; MARPAT 145:46081
GI



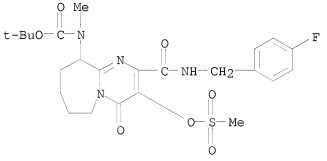
AB This patent provides a process for preparation of chiral hexahydropyrimido[1,2-a]azepine-2-carboxamides I [wherein n = 0-3; L = hydroxy protecting group; R1 = H, (un)substituted alkyl, or aryl; R2-R6 = independently H or (un)substituted alkyl; T = (un)substituted (hetero)aryl] as HIV integrase inhibitors, comprising stereoselective

hydrogenation of the corresponding enamines/imines in the presence of a rhodium metal precursor and a chiral mono- or bisphosphine ligand. For example, [2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxo-pyrimido[1,2-a]azepin-10-yl]methylcarbamic acid 1,1-dimethylethyl ester was reacted with methanesulfonyl chloride, followed by removing the BOC group, N-halogenating, and treating with DBU to give the imine/enamine intermediate. The imine/enamine obtained in the previous step was hydrogenated in trifluoroethanol in the presence of [Rh(COD)Cl]2 and Josiphos J212-1 chiral ligand, followed by reacting with activated N,N-dimethyloxamic acid in situ to give II in high yield. The title compds. are useful as HIV integrase inhibitors for treating HIV infection and AIDS (no data).

IT 857672-38-9P 857672-39-0P 857672-40-3P
857672-43-6P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of chiral hexahydropyrimido[1,2-a]azepine-2-carboxamides as HIV integrase inhibitors)

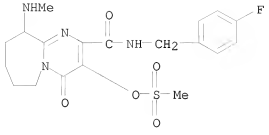
RN 857672-38-9 CAPLUS

CN Carbamic acid, [2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-[(methylsulfonyl)oxy]-4-oxopyrimido[1,2-a]azepin-10-yl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



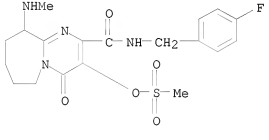
RN 857672-39-0 CAPLUS

CN Pyrimido[1,2-a]azepine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-10-(methylamino)-3-[(methylsulfonyl)oxy]-4-oxo-, hydrochloride (1:1) (CA INDEX NAME)



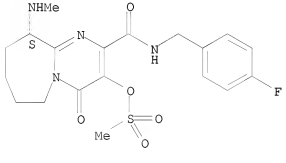
● HCl

RN 857672-40-3 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide,
N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-10-(methylamino)-3-
[(methylsulfonyl)oxy]-4-oxo- (CA INDEX NAME)



RN 857672-43-6 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide,
N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-10-(methylamino)-3-
[(methylsulfonyl)oxy]-4-oxo-, (10S)- (CA INDEX NAME)

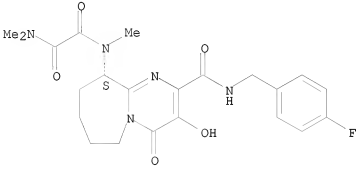
Absolute stereochemistry.



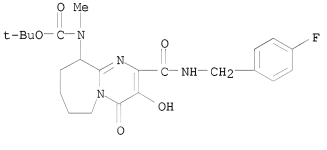
IT 724444-40-0P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP
(Preparation)
(preparation of chiral hexahydropyrimido[1,2-a]azepine-2-carboxamides as HIV

integrase inhibitors)
RN 724444-40-0 CAPLUS
CN Ethanediamide, N1-[(10S)-2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]-N1,N2,N2-trimethyl- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 724446-08-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of chiral hexahydropyrimido[1,2-a]azepine-2-carboxamides as HIV integrase inhibitors)
RN 724446-08-6 CAPLUS
CN Carbamic acid, [2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:588968 CAPLUS
DOCUMENT NUMBER: 143:115561
TITLE: Preparation of hexahydropyrimido[1,2-a]azepine-2-carboxylates for treatment of HIV and AIDS
INVENTOR(S): Askin, David; Conlon, David; Lee, Jaemoon; Pipik, Brenda; Zhong, Yong-Li; Kohmura, Yoshinori
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Banyu Pharmaceutical Co., Ltd.
SOURCE: PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005061501	A2	20050707	WO 2004-US41115	20041208
WO 2005061501	A3	20060406		
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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004303856	A1	20050707	AU 2004-303856	20041208
CA 2547159	A1	20050707	CA 2004-2547159	20041208
EP 1694678	A2	20060830	EP 2004-813437	20041208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU				
JP 2007513958	T	20070531	JP 2006-543954	20041208
IN 2006DN02443	A	20070803	IN 2006-DN2443	20060502
US 20070142635	A1	20070621	US 2006-582414	20060608

PRIORITY APPLN. INFO.: US 2003-528704P P 20031212
WO 2004-US41115 W 20041208
OTHER SOURCE(S): CASREACT 143:115561; MARPAT 143:115561
GI

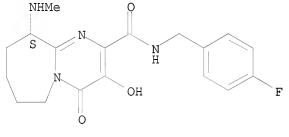
I

AB Processes for preparing 10-amino-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepine-2-carboxylates and related compds. are disclosed. The preparation of carboxamide derivs. from these carboxylates is also disclosed. The carboxamides are HIV integrase inhibitors and are useful for treating HIV infection and AIDS. E.g., I was prepared in a series of steps starting with dihydropyran.

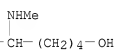
IT 724445-90-3P 724445-93-6P 724445-95-8P
724445-97-0P 724445-98-1P 724446-00-8P
724446-02-0P 724446-04-2P 724446-08-6P
724446-10-0P 724783-88-4P 857672-38-9P
857672-39-0P 857672-41-4P 857672-42-5P
857859-45-1P 958444-38-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of hexahydropyrimido[1,2-a]azepine-2-carboxylates for treatment of HIV and AIDS)

RN 724445-90-3 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-10-(methylamino)-4-oxo-, (10S)- (CA INDEX NAME)

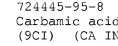
Absolute stereochemistry. Rotation (-).



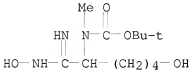
RN 724445-93-6 CAPLUS
CN Hexanenitrile, 6-hydroxy-2-(methylamino)- (CA INDEX NAME)



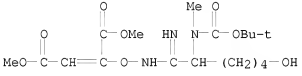
RN 724445-95-8 CAPLUS
CN Carbamic acid, (1-cyano-5-hydroxypentyl)methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



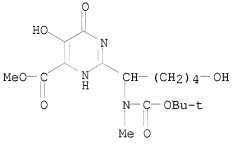
RN 724445-97-0 CAPLUS
CN Carbamic acid, [5-hydroxy-1-[(hydroxyamino)iminomethyl]pentyl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



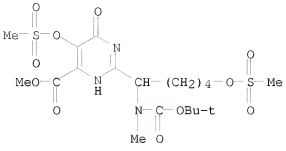
RN 724445-98-1 CAPLUS
CN 2-Butenedioic acid, 2-[[[2-[[(1,1-dimethylethoxy)carbonyl]methylamino]-6-hydroxy-1-iminohexyl]amino]oxy]-, 1,4-dimethyl ester (CA INDEX NAME)



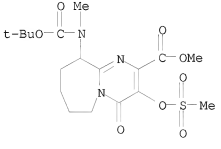
RN 724446-00-8 CAPLUS
CN 4-Pyrimidinecarboxylic acid, 2-[1-[[(1,1-dimethylethoxy)carbonyl]methylamino]-5-hydroxypentyl]-1,6-dihydro-5-hydroxy-6-oxo-, methyl ester (CA INDEX NAME)



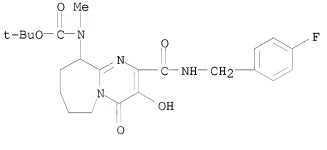
RN 724446-02-0 CAPLUS
CN 4-Pyrimidinecarboxylic acid, 2-[1-[[(1,1-dimethylethoxy)carbonyl]methylamino]-5-[(methylsulfonyl)oxy]pentyl]-1,6-dihydro-5-[(methylsulfonyl)oxy]-6-oxo-, methyl ester (CA INDEX NAME)



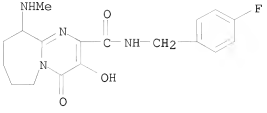
RN 724446-04-2 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxylic acid, 10-[[(1,1-dimethylethoxy)carbonyl]methylamino]-4,6,7,8,9,10-hexahydro-3-[(methylsulfonyl)oxy]-4-oxo-, methyl ester (CA INDEX NAME)



RN 724446-08-6 CAPLUS
CN Carbamic acid, [2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

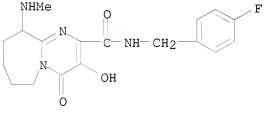


RN 724446-10-0 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-10-(methylamino)-4-oxo-, hydrochloride (1:1) (CA INDEX NAME)

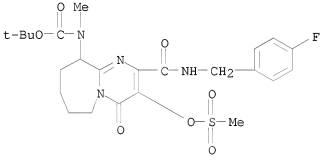


● HCl

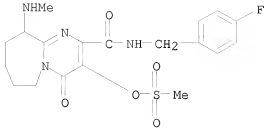
RN 724783-88-4 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-10-(methylamino)-4-oxo- (CA INDEX NAME)



RN 857672-38-9 CAPLUS
CN Carbamic acid, [2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-[(methylsulfonyl)oxy]-4-oxopyrimido[1,2-a]azepin-10-yl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



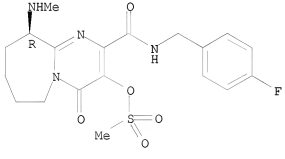
RN 857672-39-0 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-10-(methylamino)-3-[(methylsulfonyl)oxy]-4-oxo-, hydrochloride (1:1) (CA INDEX NAME)



● HCl

RN 857672-41-4 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide,
N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-10-(methylamino)-3-[(methylsulfonyl)oxy]-4-oxo-, (10R)- (CA INDEX NAME)

Absolute stereochemistry.

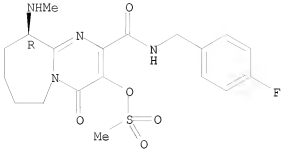


RN 857672-42-5 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, (2S,3S)-, compd. with (10R)-N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-10-(methylamino)-3-[(methylsulfonyl)oxy]-4-oxopyrimido[1,2-a]azepine-2-carboxamide (1:2) (9CI) (CA INDEX NAME)

CM 1

CRN 857672-41-4
CMF C19 H23 F N4 O5 S

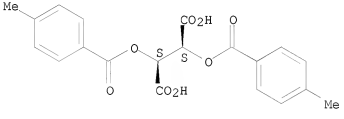
Absolute stereochemistry.



CM 2

CRN 32634-68-7
CMF C20 H18 O8

Absolute stereochemistry. Rotation (+).

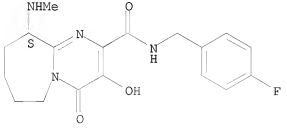


RN 857859-45-1 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, (2R,3R)-, compd. with (10S)-N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-10-(methylamino)-4-oxopyrimido[1,2-a]azepine-2-carboxamide (1:2) (9CI) (CA INDEX NAME)

CM 1

CRN 724445-90-3
CMF C18 H21 F N4 O3

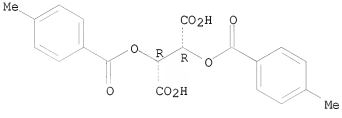
Absolute stereochemistry. Rotation (-).



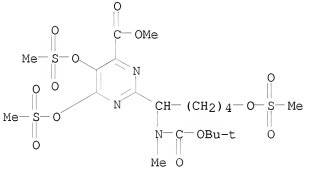
CM 2

CRN 32634-66-5
CMF C20 H18 O8

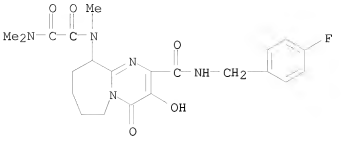
Absolute stereochemistry. Rotation (-).



RN 958444-38-7 CAPLUS
CN 4-Pyrimidinecarboxylic acid, 2-[1-[[(1,1-dimethylethoxy)carbonyl]methylamino]-5-[(methylsulfonyl)oxy]pentyl]-5,6-bis[(methylsulfonyl)oxy]-, methyl ester (CA INDEX NAME)

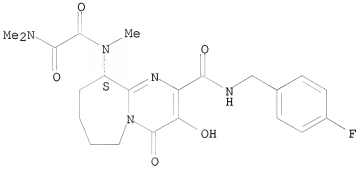


IT 724444-38-6P 724444-40-0P 724446-06-4P
857672-40-3P 857672-43-6P 857672-44-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of hexahydropyrimido[1,2-a]azepine-2-carboxylates for treatment of HIV and AIDS)
RN 724444-38-6 CAPLUS
CN Ethanediamide, N1-[2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]-N1,N2,N2-trimethyl- (CA INDEX NAME)

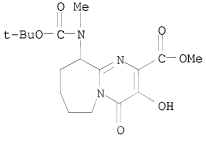


RN 724444-40-0 CAPLUS
CN Ethanediamide, N1-[(10S)-2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]-N1,N2,N2-trimethyl- (CA INDEX NAME)

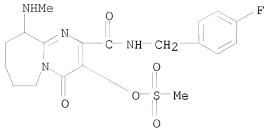
Absolute stereochemistry. Rotation (-).



RN 724446-06-4 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxylic acid, 10-[[(1,1-dimethylethoxy)carbonyl]methylamino]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxo-, methyl ester (CA INDEX NAME)

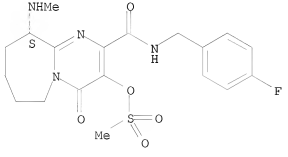


RN 857672-40-3 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-10-(methylamino)-3-[(methylsulfonyl)oxy]-4-oxo- (CA INDEX NAME)



RN 857672-43-6 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-10-(methylamino)-3-[(methylsulfonyl)oxy]-4-oxo-, (10S)- (CA INDEX NAME)

Absolute stereochemistry.

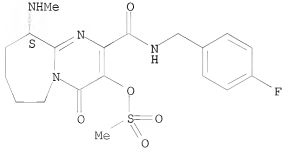


RN 857672-44-7 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, (2S,3S)-, compd. with (10S)-N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-10-(methylamino)-3-[(methylsulfonyl)oxy]-4-oxopyrimido[1,2-a]azepine-2-carboxamide (1:2) (9CI) (CA INDEX NAME)

CM 1

CRN 857672-43-6
CMF C19 H23 F N4 O5 S

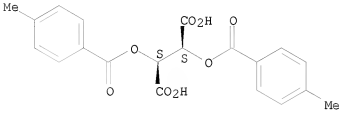
Absolute stereochemistry.



CM 2

CRN 32634-68-7
CMF C20 H18 O8

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:566604 CAPLUS
DOCUMENT NUMBER: 141:123648
TITLE: A preparation of tetrahydro-4H-pyrido[1,2-a]pyrimidine derivatives, useful as HIV integrase inhibitors
INVENTOR(S): Crescenzi, Benedetta; Kinzel, Olaf; Muraglia, Ester; Orvieto, Federica; Pescatore, Giovanna; Rowley, Michael; Summa, Vincenzo
PATENT ASSIGNEE(S): Istituto Di Ricerche Di Biologia Molecolare P. Angeletti Spa, Italy
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004058757	A1	20040715	WO 2003-GB5543	20031218
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003292437	A1	20040722	AU 2003-292437	20031218
BR 2003017749	A	20051122	BR 2003-17749	20031218
CN 1753892	A	20060329	CN 2003-80109921	20031218
CN 100343253	C	20071017		
NZ 540729	A	20080328	NZ 2003-540729	20031218
RU 2329265	C2	20080720	RU 2005-123807	20031218
ZA 2005004853	A	20061129	ZA 2005-4853	20050614
IN 2005DN02642	A	20070112	IN 2005-DN2642	20050616
MX 2005007010	A	20050818	MX 2005-7010	20050624
NO 2005003624	A	20050926	NO 2005-3624	20050726
HK 1090046	A1	20080808	HK 2006-110629	20060922

PRIORITY APPLN. INFO.:			
US 2002-436830P	P	20021227	
US 2003-528776P	P	20031212	
US 2002-463830P	P	20021227	
US 2003-258776P	P	20031212	
WO 2003-GB5543	W	20031218	

OTHER SOURCE(S): MARPAT 141:123648
GI

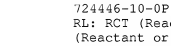
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to a preparation of tetrahydro-4H-pyrido[1,2-a]pyrimidine derivs. of formula I [wherein: X is (CH2)1-2; R1 and R2 are both H or Me; R3 is H; R4 is p-fluorobenzyl, 4-fluoro-3-methylbenzyl, 3-chlorobenzyl, or

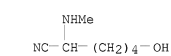
3-chloro-4-methylbenzyl; R5 is H ,N(Me)C(O)CH2SO2Me, N(Me)SO2NMe2, or -SO2-Y, etc.; Y is a N-containing 4- or 5-membered ring, or morpholinyl, etc.], useful as inhibitors of HIV integrase and inhibitors of HIV replication (no biol. data). These compds. are useful in the prevention and treatment of infection by HIV and in the prevention, delay in the onset, and treatment of AIDS. For instance, compound II was prepared via heterocyclization of 2-iminopiperidine-1-ol with di-Me acetylenedicarboxylate, thermal rearrangement of the obtained oxadiazolopyridine derivative III, and subsequent amidation of the obtained pyridopyrimidine derivative IV by 4-fluorobenzylamine (example 1).

IT 724445-93-6P 724445-95-8P 724445-97-0P
724445-98-1P 724446-00-8P 724446-02-0P
724446-04-2P 724446-06-4P 724446-08-6P
724446-10-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of pyridopyrimidine derivs., useful as HIV integrase inhibitors)

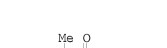
RN 724445-93-6 CAPLUS
CN Hexanenitrile, 6-hydroxy-2-(methylamino)- (CA INDEX NAME)



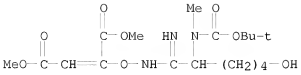
RN 724445-95-8 CAPLUS
CN Carbamic acid, (1-cyano-5-hydroxypentyl)methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



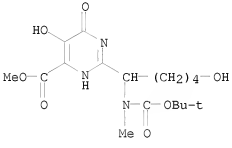
RN 724445-97-0 CAPLUS
CN Carbamic acid, [5-hydroxy-1-[(hydroxyamino)iminomethyl]pentyl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



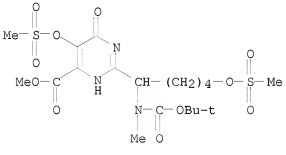
RN 724445-98-1 CAPLUS
CN 2-Butenedioic acid, 2-[[[2-[[(1,1-dimethylethoxy)carbonyl]methylamino]-6-hydroxy-1-iminohexyl]amino]oxy]-, 1,4-dimethyl ester (CA INDEX NAME)



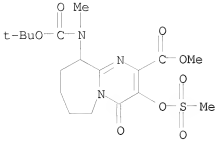
RN 724446-00-8 CAPLUS
CN 4-Pyrimidinecarboxylic acid, 2-[1-[[(1,1-dimethylethoxy)carbonyl]methylamino]-5-hydroxypentyl]-1,6-dihydro-5-hydroxy-6-oxo-, methyl ester (CA INDEX NAME)



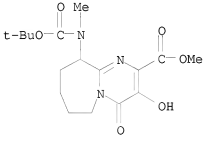
RN 724446-02-0 CAPLUS
CN 4-Pyrimidinecarboxylic acid, 2-[1-[[(1,1-dimethylethoxy)carbonyl]methylamino]-5-[(methylsulfonyl)oxy]pentyl]-1,6-dihydro-5-[(methylsulfonyl)oxy]-6-oxo-, methyl ester (CA INDEX NAME)



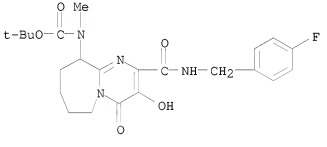
RN 724446-04-2 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxylic acid, 10-[[(1,1-dimethylethoxy)carbonyl]methylamino]-4,6,7,8,9,10-hexahydro-3-[(methylsulfonyl)oxy]-4-oxo-, methyl ester (CA INDEX NAME)



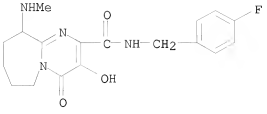
RN 724446-06-4 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxylic acid, 10-[[(1,1-dimethylethoxy)carbonyl]methylamino]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxo-, methyl ester (CA INDEX NAME)



RN 724446-08-6 CAPLUS
CN Carbamic acid, [2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

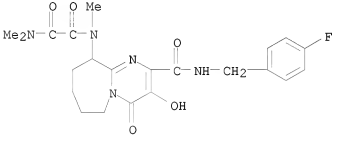


RN 724446-10-0 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-10-(methylamino)-4-oxo-, hydrochloride (1:1) (CA INDEX NAME)



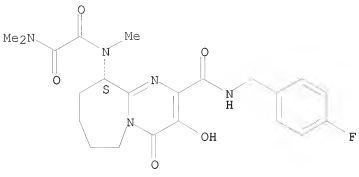
● HCl

IT 724444-38-6P 724444-40-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyridopyrimidine derivs., useful as HIV integrase inhibitors)
RN 724444-38-6 CAPLUS
CN Ethanediamide, N1-[2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]-N1,N2,N2-trimethyl- (CA INDEX NAME)

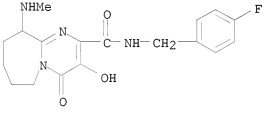


RN 724444-40-0 CAPLUS
CN Ethanediamide, N1-[(10S)-2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]-N1,N2,N2-trimethyl- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 724783-88-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of pyridopyrimidine derivs., useful as HIV integrase inhibitors)
RN 724783-88-4 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide, N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-10-(methylamino)-4-oxo- (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:566603 CAPLUS
DOCUMENT NUMBER: 141:123647
TITLE: Preparation of tetrahydro-4H-pyrido[1,2-a]pyrimidines and related compounds as HIV integrase inhibitors
INVENTOR(S): Crescenzi, Benedetta; Kinzel, Olaf; Muraglia, Ester; Orvieto, Federica; Pescatore, Giovanna; Rowley, Michael; Summa, Vincenzo
PATENT ASSIGNEE(S): Istituto Di Ricerche Di Biologia Molecolare P. Angeletti Spa, Italy
SOURCE: PCT Int. Appl., 113 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004058756	A1	20040715	WO 2003-GB5536	20031218
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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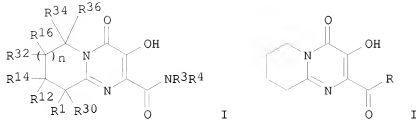
AU 2003292436	A1	20040722	AU 2003-292436	20031218
EP 1578748	A1	20050928	EP 2003-768014	20031218
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1753892	A	20060329	CN 2003-80109921	20031218
CN 100343253	C	20071017		
JP 2006513200	T	20060420	JP 2004-563339	20031218
ZA 2005004853	A	20061129	ZA 2005-4853	20050614
US 20060046985	A1	20060302	US 2005-540449	20050622
US 7414045	B2	20080819		
US 20080176869	A1	20080724	US 2008-75514	20080312

PRIORITY APPLN. INFO.:			
	US 2002-436830P	P	20021227
	US 2003-528776P	P	20031212
	WO 2003-GB5536	W	20031218
	US 2005-540449	A3	20050622

OTHER SOURCE(S): MARPAT 141:123647
GI



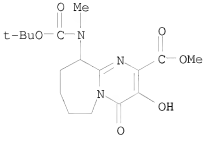
I II

AB The preparation of tetrahydro-4H-pyrido[1,2-a]pyrimidines I [R1, R12, R16 = independently H, NR2R5, OR2, SR2, S(O)R2, SO2R2, SO2NR2R5m O2CNR2R5, R11, C1-6 alkyl, SR18, SO2R18, N[SO2N(C1-6 alkyl)2]R18, etc; R2 = H, (un)substituted C1-6 alkyl, 5-6 membered heteroarom. ring; R5 = H, (un)substituted C1-6 alkyl, (un)substituted COC1-6 alkyl, COC1-6 fluoroalkyl, COR7, COCONR8R9, SO2NR8R9, SO2R7, COCOR10; NR2R5 form 4-7 membered heterocyclic ring; R7, R11 = heterocyclic ring; R8, R8 = C1-6 alkyl, aryl; R14,R30, R32, R34, R36 = independently H, (un)substituted C1-6 alkyl; R18 = substituted C1-6 alkyl; R3 = H, C1-6 alkyl; R4 = H, (un)substituted C1-6 alkyl, OC1-4 alkyl, C2-5 alkynyl, C3-8 cycloalkyl, aryl, or heteroaryl; NR3R4 = C3-7 (un)substituted azacycloalkyl ring; n = 0-3] and related compds. are described. Thus, cyclocondensation of 2-iminopiperidin-1-ol hydrochloride (prepared in 3 steps from tert-Bu benzyloxycarbamate and 5-chlorovaleronitrile) and di-Me acetylenedicarboxylate gave tetraydropyridopyrimidinecarboxylate II (R = OMe). Amidation of II (R = OMe) with 4-fluorobenzylamine gave title compound II (R = 4-CH2C6H4F). These compds. are inhibitors of HIV integrase and inhibitors of HIV replication, and useful in the prevention and treatment of infection by HIV and in the prevention, delay in the onset, and treatment of AIDS (no data). The compds. can be employed against HIV infection and AIDS as compds. per se or in the form of pharmaceutically acceptable salts. The compds. and their salts can be employed as ingredients in pharmaceutical compns., optionally in combination with other antivirals, immunomodulators, antibiotics or vaccines.

IT 724446-06-4P
RL: BYP (Byproduct); PREP (Preparation)
(preparation of tetrahydropyridopyrimidine derivs. as HIV integrase inhibitors)

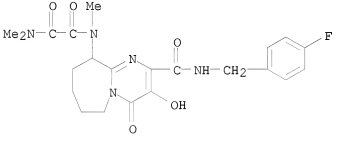
RN 724446-06-4 CAPLUS

CN Pyrimido[1,2-a]azepine-2-carboxylic acid, 10-[[(1,1-dimethylethoxy)carbonyl]methylamino]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxo-, methyl ester (CA INDEX NAME)



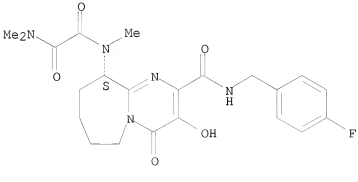
IT 724444-38-6P 724444-40-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of tetrahydropyridopyrimidine derivs. as HIV integrase inhibitors)

RN 724444-38-6 CAPLUS
CN Ethanediamide, N1-[2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]-N1,N2,N2-trimethyl- (CA INDEX NAME)



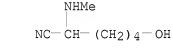
RN 724444-40-0 CAPLUS
CN Ethanediamide, N1-[(10S)-2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]-N1,N2,N2-trimethyl- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

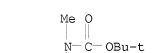


IT 724445-93-6P 724445-95-8P 724445-97-0P
724445-98-1P 724446-00-8P 724446-02-0P
724446-04-2P 724446-08-6P 724446-10-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of tetrahydropyridopyrimidine derivs. as HIV integrase inhibitors)

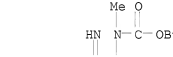
RN 724445-93-6 CAPLUS
CN Hexanenitrile, 6-hydroxy-2-(methylamino)- (CA INDEX NAME)



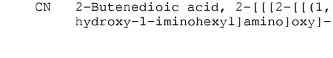
RN 724445-95-8 CAPLUS
CN Carbamic acid, (1-cyano-5-hydroxypentyl)methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



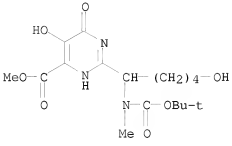
RN 724445-97-0 CAPLUS
CN Carbamic acid, [5-hydroxy-1-[(hydroxyamino)iminomethyl]pentyl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



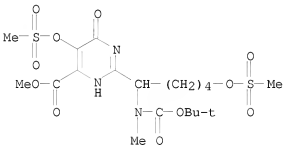
RN 724445-98-1 CAPLUS
CN 2-Butenedioic acid, 2-[[[2-[[(1,1-dimethylethoxy)carbonyl]methylamino]-6-hydroxy-1-iminohexyl]amino]oxy]-, 1,4-dimethyl ester (CA INDEX NAME)



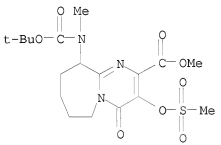
RN 724446-00-8 CAPLUS
CN 4-Pyrimidinecarboxylic acid, 2-[1-[[(1,1-dimethylethoxy)carbonyl]methylamino]-5-hydroxypentyl]-1,6-dihydro-5-hydroxy-6-oxo-, methyl ester (CA INDEX NAME)



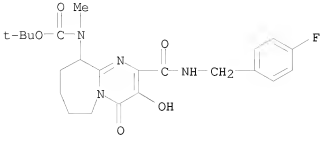
RN 724446-02-0 CAPLUS
CN 4-Pyrimidinecarboxylic acid, 2-[1-[[(1,1-dimethylethoxy)carbonyl]methylamino]-5-[(methylsulfonyl)oxy]pentyl]-1,6-dihydro-5-[(methylsulfonyl)oxy]-6-oxo-, methyl ester (CA INDEX NAME)



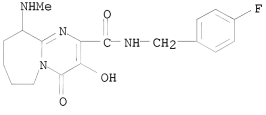
RN 724446-04-2 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxylic acid, 10-[[(1,1-dimethylethoxy)carbonyl]methylamino]-4,6,7,8,9,10-hexahydro-3-[(methylsulfonyl)oxy]-4-oxo-, methyl ester (CA INDEX NAME)



RN 724446-08-6 CAPLUS
CN Carbamic acid, [2-[[[(4-fluorophenyl)methyl]amino]carbonyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-4-oxopyrimido[1,2-a]azepin-10-yl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 724446-10-0 CAPLUS
CN Pyrimido[1,2-a]azepine-2-carboxamide,
N-[(4-fluorophenyl)methyl]-4,6,7,8,9,10-hexahydro-3-hydroxy-10-(methylamino)-4-oxo-, hydrochloride (1:1) (CA INDEX NAME)



● HCl

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT